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Concluding Remarks

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I have no intention of making a coherent summary of the 33 papers presented at the symposium. For that I would need more time and, more important, much more expertise than I have in this particularly difficult field of environmental health. Instead I would like to make some—in most cases rather general and subjective—remarks which will not necessarily follow the order of presentation of the papers. I should also like to assure those authors whose names are not mentioned here that this does not reflect on the value of their papers.

About half of the papers submitted dealt with the epidemiology of health hazards related to the plastics and synthetic rubber industries. In this respect, particularly complex is the rubber industry, where several thousand substances have been used in various combinations during the past decades, and new chemicals are being continuously introduced, together with changing working conditions. This has made the situation in each plant almost unique. The multitude of interacting factors together with varying latent periods for different biological effects tend to make detection of delayed disease, such as occupational cancer, extremely difficult. This was stressed by Dr. Mancuso's excellent presentation of his epidemiological studies in the rubber industry. In his view, the evaluation of each individual plant has real epidemiological significance. Combining the mortality data from a series of rubber plants should be avoided, because it may submerge recognition of true excess risks detected in some individual plants or in specific departments. We should keep this in mind when trying to use national mortality and morbidity data, instead of local ones, for the purposes of detecting the effects of adverse environmental conditions on health. It is also worth remembering the major concerns in the design of epidemiological studies in such complex environments as the rubber industry: the first is the year (or years) in which the cohort study is established; the second is the definition of the cohort, and the third is the use of the proper controls. Dr. Mancuso strongly advocated internal controls, i.e., comparison of employee groups within the same plant. The most difficult problem is, however, the identification of specific chemicals or combinations of chemicals in each department or process which may be of etiological significance.

Drs. Fraser and Rappaport tried to assess, both in qualitative and quantitative terms, the exposures which may occur during the curing of synthetic rubbers. Air pollutants in curing rooms result from volatilization of the components of the curing system, but new airborne substances may also be generated by chemical interactions. This makes the system extremely complex. By using a typical formulation they determined experimentally the individual compounds released from a sample of stock cured over a 20-min period. Thirty-two peaks were identified in the gas chromatogram belonging to an extremely complex mixture of compounds, in various concentrations. Other vulcanization processes would probably discharge equally complex mixtures containing residual monomers and impurities normally including oligomers, accelerators, antioxidants, and antiozonants. This example illustrates how difficult it is to obtain an exact picture of the current exposures and that it is virtually impossible to assess past exposures in different rubber industries. A different course of action is to concentrate environmental monitoring on well defined monomers such as vinyl chloride and chloroprene (Mr. Nutts' paper illustrated this approach very well) or to quantify the exposure

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by an index such as the mass of respirable particulates.

Thus there is no doubt a need for better identification and regular monitoring of the substances to which workers are exposed in the plastics industry, particularly in the smaller establishments where intermediate or semi-finished products are processed and machined. Without such information, all future epidemiological studies will suffer from the same defects as the past ones, i.e., the difficulty or impossibility of relating changes in health status to environmental conditions or to a specific chemical in which we are interested.

Other studies, such as the one by Dr. Englund on mortality and cancer morbidity in the Swedish vinyl chloride and poly (vinyl chloride) production, pointed out another problem which was apparent in smaller industries, i.e., inadequate size of the populations and the small number of cases that could be studied. This is often confounded by the inadequacies of existing registers of specific morbidity, such as cancer registers.

Despite the keen interest in the metabolism of such monomers as vinyl chloride and styrene, kinetics, distribution, elimination and metabolic transformation of these and other substances used in the plastics industry are poorly understood, both in animals and man. Dr. Watanabe and his colleagues showed that the disposition of vinyl chloride in the body was a function of the administered dose which appeared to be the result of metabolic saturation incurred at high dose levels. They suggested that a correlation exists between the doses of vinyl chloride that cause tumors and those that saturate the metabolic or detoxifying pathways, and, on the basis of different patterns of metabolites found in the urine of rats exposed to high and low doses of vinyl chloride, they deduced that a threshold must exist for the carcinogenic effect of vinyl chloride. This was disputed by Dr. Montesano because the metabolites detected in urine did not necessarily reflect the metabolism in the cells of the organ which eventually developed tumors.

There is an interesting difference between the pharmacokinetic behavior of vinyl chloride and styrene following vapor-phase exposure. Whereas a plateau equilibrium concentration directly proportional to the vapor-phase exposure concentration was observed for vinyl chloride, subsequent studies by Dr. Whitey with styrene showed that in this case the blood levels continued to rise linearly after the initial 90–120 min of exposure, the animal body behaving as a sink for the styrene monomer, probably until the lipid comparment either became saturated or the tissues reached the same concentration as the exposure atmosphere. The metabolic transformations of vinyl chloride have attracted much attention in view of the hypothesis that a metabolic intermediate, vinyl chloride epoxide, is the ultimate carcinogen. Epoxides are also formed when mixed function oxidases metabolize compounds such as styrene. Epoxides may be further metabolized to diols or thioether conjugates, resulting in detoxication. A very interesting aspect of this problem was presented by Bend and his colleagues of the NIEHS in their study on hepatic and extrahepatic metabolism of 8-^{14}C-styrene oxide, and Dr. Montesano presented new evidence that the mutagenic, and perhaps carcinogenic, activity of vinyl chloride is due to its metabolic activation to chloroethylene oxide (vinyl chloride epoxide). Using human liver biopsy samples as a tissue-mediated mutagenicity bioassay system, he showed that vinylidene chloride and chloroprene were also mutagenic following metabolic activation. Thus it appears that this new class of carcinogens exemplified by vinyl chloride behaves in a manner similar to the *N*-nitroso compounds or the aromatic amines which have to be enzymatically activated to produce adverse biological effects.

As Dr. Eckhardt pointed out in his excellent overview of occupational environmental hazards in the plastics industry, we are all most acutely aware of the carcinogenic risk associated with exposure to vinyl chloride and the possibility that tumors other than angiosarcomas of the liver may result from such exposure is being investigated in many laboratories. There are, however, other potentially serious hazards associated with some of the chemicals used in the polymer industry, as discussed, for example by Dr. Lee aand Professor Sanotskii. Thiram is a common accelerator used in rubber vulcanization. Besides causing allergic contact dermatitis, thiram is known to produce severe reactions if absorbed with alcohol or paraldehyde. Dr. Lee has shown that it is also neurotoxic in rats in doses of about 70 mg/kg/day. The effects are characterized by ataxia and paralysis of the hind legs associated with demyelination and degenerative changes. It also affects the behavior of rats. Sanotskii presented a review of experimental st dies in the USSR indicating that chloroprene has a marked effect on reproductive function and the development of offspring in mice and rats and, on the basis of this evidence and of occupational health experience, he has proposed an MAC of 0.05 mg/m^3 which is well below the established MAC in the USSR of 4 mg/m^3 and the TLV in the USA (based on skin reactions) of 90 mg/m^3. These observations certainly require attention and may eventually lead to a drastic revision of the existing TLV for chloroprene.

The small number of papers on the toxicology of various additives was conspicuous in this symposium. There are hundreds of additives used in plastics and rubber manufacture, including organotin and other metal compounds, whose toxic properties are as little known as those of flame retardants reviewed by Drs. Liepins and Pearce. The health concern with flame retardants is not only related to their manufacture, but also to possible leaching from fire-retardant fabrics. Another aspect dealt with extensively in this symposum is the toxicity of smoke from burning polymers and of the combustion products of flame retardants as presented in the excellent group of papers presented by Drs. Petajan, Einhorn, and Wright. This is a new and difficult but rapidly progressing field of toxicology of great practical interest.

The concern with the carcinogenicity of vinyl chloride in occupational exposure has its counterpart in the recent proposals to prohibit certain food packaging and food contact materials made from poly(vinyl chloride). This action is based on evidence that vinyl chloride may migrate into the food from vinyl chloride plastics. The present concern with residual monomers goes, of course, beyond vinyl chloride. Thus the Bureau of Chemical Safety of the Department of National Health and Welfare of Canada, as reported by Dr. Withey, recently became interested in the content of styrene monomer in polystyrene products and in the extent to which styrene leaches into food from polystyrene containers. Dr. Piver showed that the properties of the monomer/polymer system which influence the amount of residual monomer in the polymer as a function of time, are the diffusivity and solubility of the monomer in the polymer and the particle size of the polymer resin. Such diffusion models provide a useful framework for examination of the transport of nonreactive chemical additives from plastics.

Several other papers dealt with the safety of consumer products containing plastic materials. Dr. Wiberg gave us a Canadian view of this problem, while Drs. Zaichenko and Shakleina presented the approaches used for setting hygiene criteria for polymer materials in the Soviet Union, where systematic toxicological research into polymers and plastics dates back to 1964, when the All-Union Institute for the Hygiene and Toxicology of Pesticides, Polymers and Plastics was established in Kiev. One aspect of particular interest in their paper was the methodology used in the USSR in establishing health criteria and standards for air quality in apartments where plastics have been used in floor coverings, furniture and various appliances.

Dr. Omori presented us with an extensive review of recent experimental studies in Japan for the evaluation of potential hazards from phthalate esters used in manufacturing PVC and some other plastics usea for medical devices, food containers and packaging materials.

At the end of this three-day symposium it seems appropriate to ask whether this joint NIEHS/WHO activity has achieved its objective. My personal opinion is that it has, although it is up to the participants to pass final judgment. It was certainly useful as a forum for the exchange of new information, not only among scientists working in different groups (industry, government, university) but also in different countries. It was very gratifying to see such a massive participation from industry, but it would have been even more satisfying if we had had more papers dealing with new developments in chemistry and technology and more active participation from the representatives of industry in the discussions. In fact, if we look more closely at the objective of the symposium, i.e., to identify potential hazards from new technological developments, I am afraid that the objective was only partly achieved. Only Dr. Bebb, with his paper on rubber processing and disposal, entered into the field of technology at all. It is obvious that we cannot make much progress in identifying new or potential health hazards from technological development unless we have the close and active cooperation of industry. The place to find this information is there, and all the rest is secondhand knowledge which is usually received outdated and too late for preventive action. In order to achieve this objective, we must gradually gain mutual confidence. This cannot, of course, be achieved at one meeting, but this has been a very good beginning.